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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/714,068	11/14/2003	Meng Yang	312762002710	2630

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EXAMINER
WOOLWINE, SAMUEL C

ART UNIT	PAPER NUMBER
1637	

NOTIFICATION DATE	DELIVERY MODE
11/09/2010	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

EOfficeSD@mofo.com

Office Action Summary	Application No.	Applicant(s)	
	10/714,068	YANG ET AL.	
	Examiner	Art Unit	
	SAMUEL C. WOOLWINE	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 August 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37 and 39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status

Applicant's reply submitted 08/25/2010 is noted. Claims 37 and 39 are pending. The rejection under 35 USC 112, 2nd paragraph made in the Office action mailed 05/18/2010 is withdrawn in view of Applicant's amendment.

The rejections under 35 USC 103 are maintained and reiterated below. Applicant's arguments will be addressed following the rejections.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 37 is rejected under 35 U.S.C. 103(a) as being unpatentable over Contag et al (US 5,650,135 prior art of record) in view of Yang et al (PNAS 97(3):1206-11, February 1, 2000, cited on the IDS of 04/22/2004).

With regard to claim 37, Contag taught (column 25, line 25):

"Alternatively, an animal model for the study of putative anti-inflammatory substances can be made by making the animal transgenic for luciferase under the control of the E-selection promoter. Since E-selection is expressed at sites of inflammation, transgenic cells at sites of inflammation would express luciferase.

The system can be used to screen for anti-inflammatory substances. Inflammatory stimuli can be administered to control and experimental animals, and the effects of putative anti-inflammatory compounds evaluated by their effects on induced luminescence in treated animals relative to control animals."

This passage suggested *administering a test substance to said animal which expresses a* [light generating protein] *under the direction of a promoter of an endogenous gene, and determining the expression of said promoter via observing the presence, absence or intensity of the* [light] *generated by said* [light generating protein] *at various locations* [see above: "sites of inflammation"] *in said animal*, and further suggests *determining the expression of said endogenous promoter, via observing the presence, absence or intensity of the* [light] *generated by said* [light generating protein] *at various locations* [see above: "sites of inflammation"] *in a control laboratory animal which expresses said* [light generating protein] *under the direction of said promoter of said gene*, and further suggests *comparing the expression of said promoter determined*

in steps a) and b), wherein the expression determined in step a) is different from that in step b) when said test substance modulates said gene expression (implicitly taught by the phrase "evaluated by their effects on induced luminescence in treated animals relative to control animals").

In addition, while the cited passage taught luciferase, Contag also taught as alternatives yellow fluorescent protein (column 3, lines 2-5; column 9, lines 29-32) and green fluorescent protein (column 9, lines 29-32).

In addition, Contag also clearly taught "mammals" (see title, abstract, column 2, lines 58-62, for example). More specifically, Contag taught non-human mammals (i.e. mice; see for example figures 5 and 6).

In addition, Contag taught (column 3, lines 25-30):

"If the image can be constructed in a time short relative to the time scale at which an "unimmobilized" subject moves, the subject is inherently "immobilized" during imaging and no special immobilization precautions are required. An image from the photon emission data is then constructed."

This passage clearly suggests a situation *wherein said animal is mobile and not restrained*.

Contag did not explicitly teach an embodiment where the method described at column 25, line 25 was performed wherein a) the animal was not restrained and b) green fluorescent protein was used in place of luciferase.

The central question here is one of a "reasonable expectation of success". Would there have been a reasonable expectation of success in observing the effects of

potential anti-inflammatory compounds on, e.g., E-selectin promoter expression, as suggested by Contag, at sites such as an internal organ, using green fluorescent protein instead of luciferase?

Yang taught whole body optical imaging of mice expressing GFP in various internal organs (e.g. abstract: "Whole-body optical images showed metastatic lesions in the brain, liver and bone of B16F0-GFP that were used for real time, quantitative measurement of tumor growth in each of these organs."). See also figure 5. This indicates it was within the skill of the art to visualize internal organs expression GFP in live mice (a non-human mammal) in real-time.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the GFP taught by Yang in place of the luciferase in the method described by Contag at column 25, line 25, for the purpose of studying potential anti-inflammatory compounds at sites of inflammation in internal organs.

As Contag taught luciferase, yellow fluorescent protein and green fluorescent protein as equivalents for the purpose of his method, it would have been *prima facie* obvious to one of ordinary skill in the art to substitute one for the other, thus arriving at the limitations *fluorescent protein*, *fluorescence*, *fluorophore*, and *autofluorescent* recited in claim 37. Furthermore, one would have been motivated to avoid restraining the animal, thus allowing its movement, in order to avoid placing unnecessary stress on the animal. Finally, one would have been motivated to substitute the GFP taught by Contag in place of the luciferase, since Yang taught (page 1206, column 2, 2nd

paragraph: "However, luciferase enzymes transferred to mammalian cells require the exogenous delivery of their luciferin substrate, an essentially impractical requirement in an intact animal." In contrast, Yang taught of using GPF (page 1210, first paragraph of "Discussion"): "No contrast agents or other compounds or treatment need to be administered to the animals; only blue light illumination is necessary."

Claim 39 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lin (US 6,380,458 prior art of record) in view of Contag et al (US 5,650,135 prior art of record) and Yang et al (PNAS 97(3):1206-11, February 1, 2000, cited on the IDS of 04/22/2004).

Lin taught the creation of genetically modified zebrafish expressing green fluorescent protein (column 7, line 11: "A preferred reporter protein that can be directly detected is the green fluorescent protein (GFP).").

Lin also taught (column 11, lines 10-18):

"The disclosed transgenic fish can be used in combination with these and other mutations to assess the effect of a mutant gene on the expression of a gene of interest. For example, mutations can be introduced into strains of transgenic fish harboring an exogenous construct containing the expression sequences of a fish gene of interest operably linked to a sequence encoding a reporter protein. By comparing the expression of the reporter protein in fish with a mutation to those without the mutation, the effect of the mutation on the expression of the gene from which the expression sequences are derived can be assessed." By "mutations can be introduced into strains

of transgenic fish", one of skill in the art would have understood that, in order to introduce the mutation to a strain of fish, the mutation would have to be introduced into the germ line (otherwise there would be one fish, not a strain, with the mutation in one cell, which would not have been realistically suitable for "comparing the expression of the reporter protein in fish with a mutation to those without the mutation").

Lin did not teach that the animals were non-human mammals, or that they were not restrained during observation.

Contag taught imaging light generating compounds including yellow and green fluorescent proteins (see abstract; column 9, lines 29-32).

In addition, Contag also clearly taught "mammals" (see title, abstract, column 2, lines 58-62, for example). More specifically, Contag taught non-human mammals (i.e. mice; see for example figures 5 and 6).

In addition, Contag taught (column 3, lines 25-30):

"If the image can be constructed in a time short relative to the time scale at which an "unimmobilized" subject moves, the subject is inherently "immobilized" during imaging and no special immobilization precautions are required. An image from the photon emission data is then constructed."

This passage clearly suggests a situation *wherein said animal is mobile and not restrained*.

The central question here is one of a "reasonable expectation of success". Would there have been a reasonable expectation of success in substituting mice

expressing GFP in place of the fish expressing GFP in the method taught by Lin, and to observe GFP expression in internal organs?

Yang taught whole body optical imaging of mice expressing GFP in various internal organs (e.g. abstract: "Whole-body optical images showed metastatic lesions in the brain, liver and bone of B16F0-GFP that were used for real time, quantitative measurement of tumor growth in each of these organs."). See also figure 5. This indicates it was within the skill of the art to visualize internal organs expression GFP in live mice (a non-human mammal) in real-time.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute mice for fish in the method of Lin. One would have been motivated to do so because mice were a well-known experimental animal. Furthermore, this would have allowed study of, for example, lung-specific gene expression, which obviously would not have been possible using fish as a model organism. Hence, mice would have allowed one to study gene expression patterns in the lungs in response to various mutations when practicing Lin's method.

Claim 37 is rejected under 35 U.S.C. 103(a) as being unpatentable over Contag et al (US 5,650,135 prior art of record) in view of Tan et al (US 6,251,384).

With regard to claim 37, Contag taught (column 25, line 25):

"Alternatively, an animal model for the study of putative anti-inflammatory substances can be made by making the animal transgenic for luciferase under the

control of the E-selection promoter. Since E-selection is expressed at sites of inflammation, transgenic cells at sites of inflammation would express luciferase.

The system can be used to screen for anti-inflammatory substances. Inflammatory stimuli can be administered to control and experimental animals, and the effects of putative anti-inflammatory compounds evaluated by their effects on induced luminescence in treated animals relative to control animals."

This passage suggested *administering a test substance to said animal which expresses a* [light generating protein] *under the direction of a promoter of an endogenous gene, and determining the expression of said promoter via observing the presence, absence or intensity of the* [light] *generated by said* [light generating protein] *at various locations* [see above: "sites of inflammation"] *in said animal*, and further suggests *determining the expression of said endogenous promoter, via observing the presence, absence or intensity of the* [light] *generated by said* [light generating protein] *at various locations* [see above: "sites of inflammation"] *in a control laboratory animal which expresses said* [light generating protein] *under the direction of said promoter of said gene*, and further suggests *comparing the expression of said promoter determined in steps a) and b), wherein the expression determined in step a) is different from that in step b) when said test substance modulates said gene expression* (implicitly taught by the phrase "evaluated by their effects on induced luminescence in treated animals relative to control animals").

In addition, while the cited passage taught luciferase, Contag also taught as alternatives yellow fluorescent protein (column 3, lines 2-5; column 9, lines 29-32) and green fluorescent protein (column 9, lines 29-32).

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Contag did not explicitly teach an embodiment where the method described at column 25, line 25 was performed wherein a) the animal was not restrained and b) green fluorescent protein was used in place of luciferase.

The central question here is one of a "reasonable expectation of success". Would there have been a reasonable expectation of success in observing the effects of potential anti-inflammatory compounds on, e.g., E-selectin promoter expression, as suggested by Contag, at sites such as an internal organ, using green fluorescent protein instead of luciferase?

Tan taught that GFP producing tumors could be excised and observed for fluorescence (column 3, lines 9-14). Tan also taught that sometimes it was not necessary to remove organ tissues; rather the fluorescence could be visualized in the whole animal by real time fluorescence optical tumor imaging (column 3, lines 15-18). At column 5, line 30, Tan stated: "In some cases the tumors are sufficiently bright that opening the animal is unnecessary—they can be seen directly through the skin." In a working example involving mice, Tan disclosed (column 12, lines 13-15): "In some cases, abdominal opening is unnecessary as the intraperitoneal tumors can be visualized through intact skin."

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute the GFP taught by Tan in place of the luciferase in the method described by Contag at column 25, line 25, for the purpose of studying potential anti-inflammatory compounds at sites of inflammation in internal organs.

As Contag taught luciferase and green fluorescent protein as equivalents for the purpose of his method, it would have been *prima facie* obvious to one of ordinary skill in the art to substitute one for the other, thus arriving at the limitations *fluorescent protein*, *fluorescence*, *fluorophore*, and *autofluorescent* recited in claim 37. Furthermore, one would have been motivated to avoid restraining the animal, thus allowing its movement, in order to avoid placing unnecessary stress on the animal. Finally, one would have been motivated to substitute the GFP in place of the luciferase, since GFP does not

require any additional compounds (such as luciferin) to be administered to the animals in order to produce fluorescence.

Claim 39 is rejected under 35 U.S.C. 103(a) as being unpatentable over Lin (US 6,380,458 prior art of record) in view of Contag et al (US 5,650,135 prior art of record) and Tan et al (US 6,251,384).

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Lin also taught (column 11, lines 10-18):

"The disclosed transgenic fish can be used in combination with these and other mutations to assess the effect of a mutant gene on the expression of a gene of interest. For example, mutations can be introduced into strains of transgenic fish harboring an exogenous construct containing the expression sequences of a fish gene of interest operably linked to a sequence encoding a reporter protein. By comparing the expression of the reporter protein in fish with a mutation to those without the mutation, the effect of the mutation on the expression of the gene from which the expression sequences are derived can be assessed." By "mutations can be introduced into strains of transgenic fish", one of skill in the art would have understood that, in order to introduce the mutation to a strain of fish, the mutation would have to be introduced into the germ line (otherwise there would be one fish, not a strain, with the mutation in one

cell, which would not have been realistically suitable for "comparing the expression of the reporter protein in fish with a mutation to those without the mutation").

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It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to substitute mice for fish in the method of Lin. One would have been motivated to do so because mice were a well-known experimental animal. Furthermore, this would have allowed study of, for example, lung-specific gene expression, which obviously would not have been possible using fish as a model organism. Hence, mice would have allowed one to study gene expression patterns in the lungs in response to various mutations when practicing Lin's method.

Response to Arguments

Applicant's arguments filed 08/25/2010 have been fully considered but they are not persuasive. Applicant argues (page 4 of response): "Contag, while mentioning green fluorescent protein in passing, clearly demonstrates only the use of luciferase to envision expression controlled by an endogenous promoter." This argument is not persuasive because Contag clearly taught that fluorescent proteins such as GFP or YFP could be used as the light generating moieties (column 9, lines 29-32). Applicant also argues that Contag teaches away from fluorescent proteins, citing to column 9, line

62 through column 10, line 6 (regarding background), and to column 8, line 35 (regarding use of green or blue wavelengths and the absorption of such). This argument is also not persuasive because, while Contag may teach an advantage of using luciferase as opposed to green fluorescent protein, it is well-established that "[d]isclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments" (see MPEP 2123-II and caselaw cited therein). Contag cannot be said to simultaneously teach the use of GFP and at the same time "teach away" from using it.

Applicant also argues that "a review of the examples set forth in Contag clearly reveals that the circumstances under which 'an image can be constructed in a time short relative to the timescale at which the immobilized subject moves' has not been realized or taught. At best this is wishful thinking." This argument is not persuasive because, while Contag may not have performed any working examples using live, unrestrained mice, he clearly suggested doing so. The issue is "reasonable expectation of success" in detecting GFP in living, unrestrained mammals. If what Contag taught was "wishful thinking", this "wishful thinking" was realized in the secondary references relied upon in the rejections. On this issue, Applicant argues that the secondary references (Yang et al, Tan et al) do not provide this reasonable expectation of success.

Applicant argues that "Yang is concerned with imaging tumors which have been constructed of cells that are deliberately prepared to express large amounts of fluorescent protein" (page 5 of response). Applicant then asserts: "The invention method, on the other hand, relies on expression controlled by endogenous promoters

which are not designed to provide high level expression of a single protein in any particular cell...Whole body fluorescent imaging of tumors artificially altered to ensure high level expression of GFP is vastly different from measuring the comparatively feeble levels of expression that would be engendered by endogenous gene promoters."

The Examiner looked to Applicant's disclosure; there are no working examples of "endogenous" promoters (i.e. promoters derived from genes of the host animal in which the imaging is taking place). There are two working examples (Examples 1 and 2) that relied on the CMV (cytomegalovirus) promoter to drive the expression of GFP. That is, animals were infected with viruses designed to express GFP in the infected host cells, under the control of the CMV promoter. What can be said of this "not endogenous" promoter?

Ma et al (US 2009/0111099, paragraph [0156]): "As expected, the viral CMV promoter appeared to be the strongest, a fact, which is well-documented in the scientific literature (U.S. Pat. Nos. 5,168,062 and 5,385,839; Cayer et al J Immunol Methods. Apr. 30, 2007;322(1-2):118-27; Sakurai et al Gene Ther. October 2005;12(19):1424-33; Fabre et al. J Gene Med. May 2006;8(5):636-45.)."

Otte et al (US 2008/0227199, paragraph [0106]): "The CMV promoter is considered the strongest available, so it is preferably chosen for the bicistronic gene in order to obtain the highest possible product yield." Also at paragraph [0190]: "Some viral promoters have these properties; the promoter/enhancer of the cytomegalovirus immediate early gene (" CMV promoter") is generally regarded as the strongest

promoter in common biotechnological use (Boshart et al., 1985, Doll et al., 1996, Foecking & Hofstetter, 1986)."

Boshart et al (Cell 41:521-530, June 1985, abstract): "It is the strongest enhancer we have analyzed so far, a property that makes it a useful component of eukaryotic expression vectors."

Iversen (US 2006/0121010, paragraph [0171]): "The CMV promoter is the strongest identified thus far and as a result, it is useful in DNA vaccine construction (Roth, J. et al., J Natl Cancer Inst 89: 21-39, 1997)."

Peng et al (US 2006/0115456, paragraph [0055]): "The CMV promoter is one of the strongest enhancer/promoters known and is active in abroad range of cell types (see, e.g., Chapman et al., Nuc. Acids Res. 19:3979-3986, 1991; and U.S. Pat. No. 5,688,688)."

Loser et al (J. Virol. 72(1):180-190, January 1998, page 180 column 1): "Since the human cytomegalovirus (CMV) major immediate-early promoter/enhancer (8) (hereafter referred to as the CMV promoter) is considered to be one of the strongest promoters in vitro, it has been used for in vivo expression of reporter and therapeutic genes by many investigators."

In short, Applicant's examples employing the CMV promoter provide no more expectation of success in "measuring the comparatively feeble levels of gene expression" from endogenous promoters than Yang or Tan do with their highly expressing tumor cells. Applicant is arguing that Yang and Tan do not provide

reasonable expectation of success, since their systems were *designed* to produce high levels of GFP. Yet Applicant's Examples 1 and 2 were clearly *also designed* to do this.

For the reasons discussed above, the arguments presented by Applicant are not persuasive, the prior art is considered to provide as much expectation of success as Applicant's disclosure, and the rejections are maintained.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SAMUEL C. WOOLWINE whose telephone number is (571)272-1144. The examiner can normally be reached on Mon-Fri 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Samuel Woolwine/
Primary Examiner